

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17974 A1

(51) International Patent Classification⁷: C07D 233/64

(21) International Application Number: PCT/KR00/01016

(22) International Filing Date:
6 September 2000 (06.09.2000)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
1999/37652 6 September 1999 (06.09.1999) KR
2000/4278 28 January 2000 (28.01.2000) KR

(71) Applicant (for all designated States except US): LG
CHEMICAL LTD. [KR/KR]; 20, Yoido-dong, Yong-
dungpo-ku, Seoul 150-010 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SHIN, Hyun-Ik
[KR/KR]; LG Apt. 8-207, Doryong-dong, Youseong-ku,
Daejeon 305-340 (KR). CHANG, Jay-Hyok [KR/KR];
LG Dormitory 3-313, 386-1, Doryong-dong Youseong-ku,
Daejeon 305-340 (KR). LEE, Kyoo-Woong [KR/KR];
LG Apt. 3-303, 386-1, Doryong-dong, Youseong-ku,
Daejeon 305-340 (KR). LEE, Hyun-II [KR/KR]; LG Apt.
6-303, Doryong-dong, Youseong-ku, Daejeon 305-340

(KR). KIM, Sung-Kee [KR/KR]; LG Apt. 9-303, Dory-
ong-dong, Youseong-ku, Daejeon 305-340 (KR). NAM,
Do-Hyun [KR/KR]; Expo Apt. 508-603, Jeonmin-dong,
Youseong-ku, Daejeon 305-390 (KR).

(74) Agent: CHOI, Kyu-Pal; 824-11, Yeoksam-dong, Kang-
nam-ku, Seoul 135-080 (KR).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING A 1-SUBSTITUTED 5-HYDROXYMETHYL IMIDAZOLE

(57) Abstract: The present invention relates to a process for preparing a 1-substituted 5-hydroxymethylimidazole of formula (1). According to the present invention, the desired compound can be prepared more safely, more rapidly and more purely in higher yield than prior art process.

BEST AVAILABLE COPY

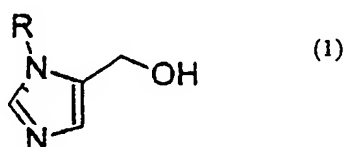
WO 01/17974 A1

PROCESS FOR PREPARING A 1-SUBSTITUTED 5-HYDROXYMETHYLIMIDAZOLE

TECHNICAL FIELD

5

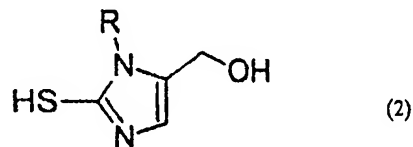
The present invention relates to a process for preparing a 1-substituted 5-hydroxymethylimidazole of the formula:



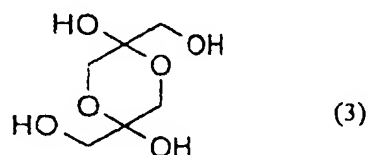
, wherein

R represents alkyl, hydroxyalkyl, allyl, or substituted or unsubstituted arylmethyl
10 or diarylmethyl, and preferably, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, allyl, benzyl, substituted
benzyl such as halogen-substituted benzyl or 3,4-dioxymethylenebenzyl, or 2-arylmethyl.

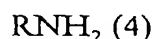
More specifically, the present invention relates to a process for preparing
compound of the above formula (1) from a 1-substituted 2-mercapto-5-
hydroxymethylimidazole of the formula:



15 , wherein R is as defined above, which is prepared by reacting 1,3-
dihydroxyacetone dimer of the formula:



, with an acid addition salt of amine of the formula:



, wherein R is as defined above, and

20

thiocyanate of the formula:

M-SCN (5)

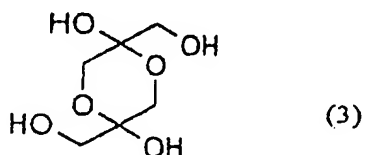
, wherein M represents alkali metal, in the presence of a transition metal catalyst such as tungstic acid, etc. and an oxidizing agent.

5

BACKGROUND ART

The 1-substituted 5-hydroxymethylimidazole of the formula (1) and its intermediate, i.e. 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) are key intermediates known to be useful for preparing various anticancer agents under development, especially, farnesyl transferase inhibitors[J. S. Ko, et al., PCT WO99/05117 A1 19990204, p129].

Various processes for the preparation of the compound of the formula (2) have already been known in the literature. For example, according to the process disclosed in EP146228B1, 1985, the 1-substituted 2-mercapto-5-hydroxymethylimidazole is obtained in the yield of 68.2% as a pale brown powder by reacting 1,3-dihydroxyacetone dimer of the formula:



, as the starting material, with amine of the formula:

RNH_2 (4)

, wherein R represents alkyl, allyl, arylmethyl or diarylmethyl, and thiocyanate of the formula:

20

M-SCN (5)

, wherein M represents potassium,

in the mixture of an organic acid and a lower alcohol solvent.

25

However, under the above reaction conditions, there are some problems associated with the isolation of the product in good purity since an unidentified black tar is formed as a by-product and turned out to be difficult to purify.

For preparing compound of the formula (1) from compound of the formula (2), the known process, an oxidative desulfurization is conventionally performed by warming compound of the formula (2) in the presence of concentrated nitric acid, with or without the catalytic amount of nitrite[R. G. Jones, J. Amer. Chem. Soc., 1949, 71, 383]. This method is useful in the laboratory scale preparation. However, this process has some problems associated with safety in the industrial scale. These are evolution of environmentally toxic nitrogen oxide gas and difficult control of the reaction. In addition, if the compound of the formula (2) has an aromatic functionality, electrophilic aromatic nitration reaction on the aromatic ring is accompanied as a side reaction.

DISCLOSURE OF THE INVENTION

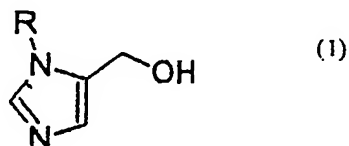
The present inventors performed extensive studies to develop a novel process for the preparation of a 1-substituted 5-hydroxymethylimidazole and its intermediate, a 1-substituted 2-mercapto-5-hydroxymethylimidazole. As a result, they have identified that the problems of the previous process for preparing compound of the formula (2) could be removed by replacing amine by its acid addition salt. That is, if the acid addition salt of amine such as ammonium chloride is used, the formation of the colored by-products are eradicated completely. Therefore, the desired compound, compound of the formula (2), can be obtained in high purity and yield.

In addition, since there are few practical examples of oxidative cleavage of thiol group, which allows to prepare compound of the formula (1) from compound of the formula (2), the present inventors made a research to develop a new process which could be viable in the industrial scale. Finally, they have identified that the desired imidazole derivative can be obtained in high purity under safe and environmentally benign reaction conditions by employing a transition metal catalyst and an oxidizing agent such as hydrogen peroxide and thus, completed the present invention.

DETAILED DESCRIPTION OF THE INVENTION

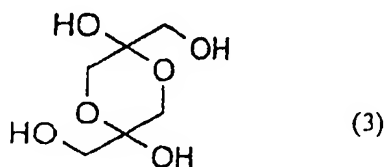
Therefore, an object of the present invention is to provide a new process for the preparation of a 1-substituted 5-hydroxymethylimidazole of the formula (1) from 1-substituted 2-mercapto-5-hydroxymethyl imidazole of the formula (2).

The present invention relates to a process for preparing 1-substituted 5-hydroxymethylimidazole of the formula:

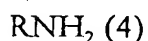


, wherein R represents alkyl, hydroxyalkyl, allyl, or substituted or unsubstituted arylmethyl or diarylmethyl, and preferably, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, allyl, benzyl, substituted benzyl such as halogen-substituted benzyl or 3,4-dioxymethylenebenzyl, or 2-arylmethyl,

comprising the steps of reacting 1,3-dihydroxyacetone dimer of the formula:



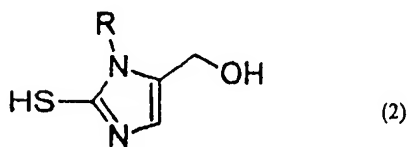
, with an acid addition salt of amine of the formula:



, wherein R is as defined above, and thiocyanate of the formula:



, wherein M represents alkali metal, in the presence of an acid catalyst in a lower alcohol solvent to prepare a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula:



, wherein R is as defined above; and,

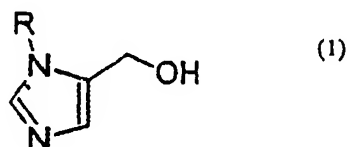
reacting the compound of the formula (2) in the presence of a transition metal catalyst and an oxidizing agent in a solvent.

As for the substituent "R", however, any conventional substituents other than those
5 as mentioned above may be applied without any explicit indication.

The term "alkyl" as used herein includes straight or branched chain alkyl.

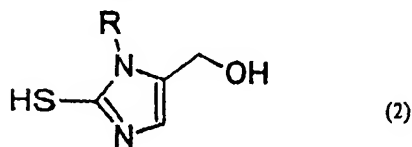
The preparation process according to the present invention comprises 2 steps. The first step is that a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) is prepared by reacting 1,3-dihydroxyacetone dimer of the formula (3) with an acid
10 addition salt of amine of the formula (4) and thiocyanate of the formula (5). The second step is that a 1-substituted 5-hydroxymethylimidazole of the formula (1) is prepared from the above compound of the formula (2) via oxidative desulfurization.

Therefore, the present invention relates to a process for preparing a 1-substituted 5-hydroxymethylimidazole of the formula:



15 , wherein R is as defined above,

by the reaction of compound of the formula:

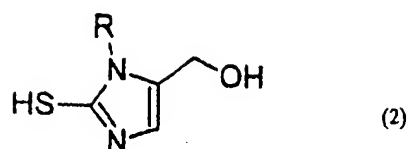


, wherein R is as defined above,

in the presence of a transition metal catalyst and an oxidizing agent in a solvent.

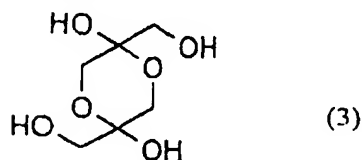
20 Hereinafter, each step of the present process will be explained in detail.

In Step 1, a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula :

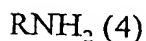


, wherein R is as defined above,

is prepared by reacting 1,3-dihydroxyacetone dimer of the formula:



, with an acid addition salt of amine of the formula:



, wherein R is as defined above, and

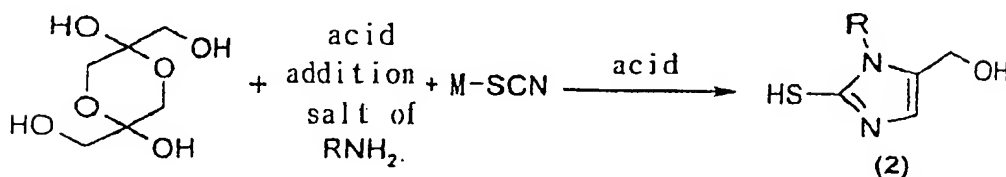
thiocyanate of the formula:



, wherein M is as defined above,

in the presence of an acid catalyst in a lower alcohol solvent.

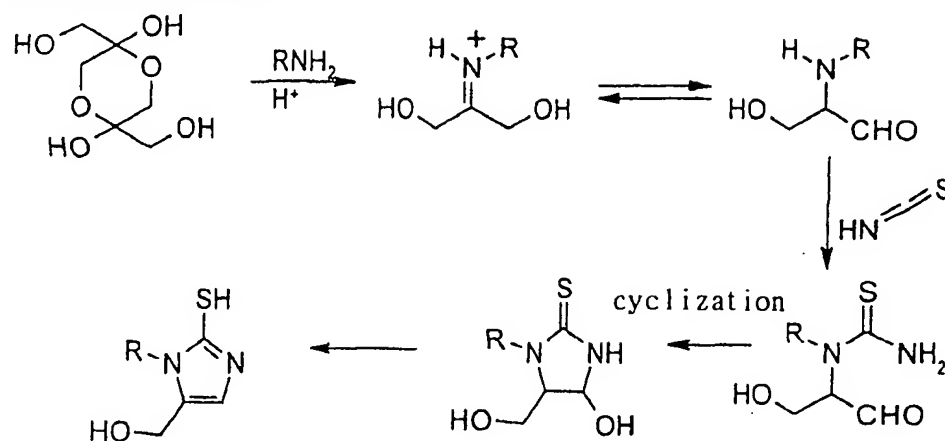
The above reaction is depicted in the following Reaction Scheme (1):



, wherein M and R are each as defined above.

The formation mechanism of imidazole compound of the formula (2) is depicted below(vide infra). Iminium intermediate is formed from dihydroxyacetone and amine, and tautomerized to α -aminoaldehyde intermediate, which reacts with thiocyanate to give urea intermediate. Intramolecular cyclization and dehydration should afford compound of the formula (2).

Reaction Scheme (2)



In the above reaction scheme, R is as defined above.

Since it is assumed that impurity material should be formed by the reaction of reactive α -aminoaldehyde intermediate and excessive amine, control of the concentration of free amine in a suitable level is thought to be the key factor for clean reaction. Therefore, in the present invention, the problems of the previous method are removed by lowering the concentration of free amine by the employment of an acid addition salt of amine.

10

More specifically, to prepare a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2), 1,3-dihydroxyacetone dimer of the formula (3), an acid addition salt of amine of the formula (4) and thiocyanate of the formula (5) are mixed in a mixture of lower alcohol and organic acid.

15

In the above reaction, the molar ratio of the 1,3-dihydroxyacetone dimer of the formula (3) to the acid addition salt of amine of the formula (4) is 0.5 ~ 2:1, preferably, 1 ~ 1.5:1. The molar ratio of the thiocyanate of the formula (5) to the acid addition salt of amine of the formula (4) is 1 ~ 3:1, preferably, 1 ~ 2:1.

As the acid addition salt of amine of the formula (4) in the above reaction, ammonium halide is preferable and ammonium chloride is most preferable. In addition, as thiocyanate of the formula (5), potassium thiocyanate is preferable.

20

The acid addition salt of amine of the formula (4) in the above reaction may be

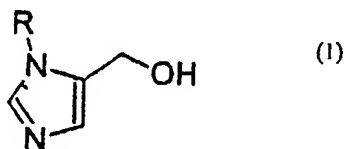
commercially available or prepared with ease according to the known procedure. In some cases, it can be prepared by introducing hydrohalogen gas into amine in an equimolar amount.

As the reaction solvent, straight or branched chain lower alcohol having from 1 to 4 carbon atom(s), or a mixture thereof is preferable. More preferably, iso-propanol or n-butanol may be used.

As the reaction catalyst, acetic acid, propionic acid or any other conventional organic acids may be used preferably.

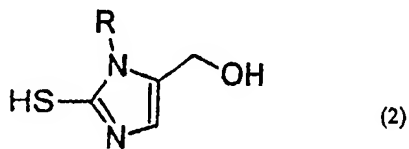
The reaction temperature may be 10 to 100 °C, preferably 20 to 80 °C.

In Step 2, a 1-substituted 5-hydroxymethylimidazole of the formula:



, wherein R is as defined above,

is prepared by reacting a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula:



, wherein R is as defined above,

in the presence of a transition metal catalyst and an oxidizing agent such as hydrogen peroxide, etc. in a solvent.

The above reaction step is explained more specifically as follows.

A 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) is reacted in the presence of oxidizing agent and the catalytic amount of transition metal in water, any other aqueous solvent or a mixture thereof at room temperature or the elevated temperature. In accordance with the above process, the 1-substituted 2-mercapto-5-

hydroxy -methylimidazole can be converted into a 1-substituted 5-hydroxymethyl imidazole of the formula (1) with ease.

As the catalyst to be used in the above step, several transition metals with oxidizing ability such as vanadium, chromium, molybdenum, manganese, tungsten, rhenium, ruthenium, osmium, etc. may be used. Among them, rhenium, ruthenium, osmium, etc. have a drawback due to their high cost, and vanadium, chromium, manganese, tungsten, etc. are preferable because of their relatively low cost. More preferable is tungstic acid (H_2WO_4), vanadium pentoxide (V_2O_5) or vanadyl sulfate (VOSO_4). The molar ratio of the transition metal catalyst such as tungstic acid (H_2WO_4), vanadium pentoxide (V_2O_5) or vanadyl sulfate (VOSO_4) to the compound of the formula (2) is generally 0.001 ~ 0.2:1, preferably 0.001 ~ 0.02:1.

As the useful oxidizing agent in the present invention, hydrogen peroxide, alkyl hydrogen peroxide (such as t-butyl hydrogen peroxide etc.) or alkaline hypochlorite (sodium or calcium salt) is preferable. More preferable is 10 ~ 30% hydrogen peroxide. They are used in an amount of 3 to 10 molar equivalents with respect to compound of the formula (1).

As the reaction solvent, water or any other aqueous solvent, preferably, lower alcohol or a mixture thereof may be used. The most preferable is water, methanol, ethanol or a mixture thereof.

The reaction temperature may be 20 to 100 °C, preferably 40 to 70 °C, more preferably 50 to 70 °C. Generally, the reaction is performed until a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) is completely converted into a 1-substituted 5-hydroxymethylimidazole of the formula (1), preferably, for 2 to 6 hours.

25

Upon the completion of the reaction, the reaction mixture may be simply neutralized and then, the resulting solid may be filtered. Alternatively, the reaction mixture may be extracted with a suitable solvent such as dichloromethane or chloroform and if necessary, further purified by treatment with a suitable solvent such as n-hexane or isopropyl ether. Accordingly, the desired compound, i.e., 1-substituted 5-

30

hydroxymethylimidazole of the formula (1) may be easily recovered from the reaction mixture in high purity.

This invention will be better understood from the following examples.
5 However, one skilled in the art will readily appreciate the specific materials and results described are merely illustrative of, and are not intended to, nor should be intended to, limit the invention as described more fully in the claims which follow thereafter.

<Step 1: Synthesis of a 1-substituted 2-mercapto-5-hydroxymethyl -imidazole>

10

Example 1: Synthesis of 1-benzyl-2-mercapto-5-hydroxymethylimidazole

Benzylammonium chloride(14.36 g, 0.1 mol) and 1,3-dihydroxyacetone dimer(18 g, 0.1 mol) were suspended in 100 ml of isopropanol and then, potassium thiocyanate(14.6 g, 0.15 mol) was added thereto. To the above suspension was added
15 dropwise acetic acid(19.22 g, 0.32 mol) and the mixture was stirred at room temperature for 24 hours. To the above mixture was added 50 ml of distilled water. The whole mixture was further stirred for 30 minutes, filtered and washed twice with 50 ml of distilled water and 50 ml of isopropyl ether, respectively, to obtain a white solid powder. The obtained powder was dried for 3 hours to give 20.4 g(Yield 92.6%) of 1-benzyl-2-
20 mercapto-5-hydroxymethylimidazole.

¹H NMR(500MHz, DMSO-d₆) δ 12.15(1H, s), 7.32(2H, t, J=7.3Hz), 7.26(1H, d, J=7.3Hz), 7.24(2H, t, J=7.3Hz), 6.85(1H, s), 5.32(2H, s), 5.25(1H, s), 4.14(2H, d, J=5Hz)

HPLC: 99.6%

25 **Example 2: Synthesis of 1-ethyl-2-mercapto-5-hydroxymethylimidazole**

Ethylammonium chloride(8.16 g, 0.1 mol) and 1,3-dihydroxyacetone dimer(18 g, 0.1 mol) were suspended in 70 ml of isopropanol and then, potassium thiocyanate(14.6 g, 0.15 mol) was added thereto. To the above suspension was added dropwise acetic acid(19.22 g, 0.32 mol) and the mixture was stirred at room temperature for 24 hours. To
30 the above reaction solution was added 50 ml of distilled water. The whole mixture was

further stirred for 30 minutes, filtered and washed twice with 50 ml of distilled water and 50 ml of isopropyl ether, respectively, to obtain a white solid powder. The obtained powder was dried for 3 hours to give 12.8 g (Yield 81.0%) of 1-ethyl-2-mercapto-5-hydroxymethylimidazole.

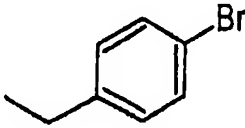
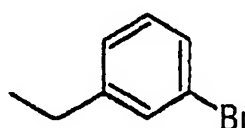
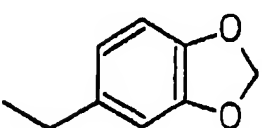
¹H NMR(500MHz, DMSO-d₆) δ 11.94(1H, s) 6.78(1H, s) 5.20(1H, s, -OH) 4.33(2H, s) 4.00(2H, q, J=7.2Hz) 1.21(3H, t, J=7.2Hz)

HPLC: 99.1%

Examples 3 ~ 5: Synthesis of 2-mercaptoimidazole derivatives

Several 2-mercaptoimidazole derivatives were synthesized according to the substantially same procedure as Example 1. The results were shown in the following Table 1.

Table 1: 2-mercaptoimidazole derivatives

Ex. No.	R	Reaction Time	Yield	¹ H NMR
3		15	91%	12.18(1H, s) 7.51(2H, d, J=8.7Hz) 7.20(2H, d, J=8.7Hz) 6.86(1H, s) 5.28(2H, s and 1H, -OH) 5.16(2H, d, J=3.7Hz)
4		15	88%	12.20(1H, s) 7.45(1H, d, J=7.8Hz) 7.44(1H, s) 7.29(1H, t, J=7.8Hz) 7.22(1H, d, J=7.8Hz) 6.88(1H, s) 5.81(2H, s and 1H, s, -OH) 4.17(2H, s)
5		22	96%	12.16(1H, s) 6.89(1H, d, J=1.8Hz) 6.85(1H, d, J=7.8Hz) 6.83(1H, s) 6.75(1H, dd, J1=7.8Hz, J2=1.8Hz) 5.98(2H, s) 5.31(1H, s, -OH) 5.21(2H, s) 4.17(2H, s)

Example 6: Synthesis of 1-allyl-2-mercapto-5-hydroxymethylimidazole

Allylammonium chloride(0.1 mol) was reacted for 23 hours according to the

substantially same procedure as Example 1. Then, 40 ml of distilled water was added thereto and the reaction mixture was distilled under reduced pressure to 1/3 volume. The precipitate was filtered, washed twice with 30 ml of distilled water and 30 ml of isopropyl ether, respectively, and dried to give 12.5 g (Yield 72.6%) of the title compound as a white powder.

^1H NMR (500MHz, DMSO- d_6) δ 12.03(1H, s), 6.81(1H, s), 5.89(1H, m), 5.21(1H, -OH), 5.12(1H, dd, $J_1=10.5\text{Hz}$, $J_2=1.4\text{Hz}$), 4.97(1H, dd, $J_1=14.4\text{Hz}$, $J_2=1.4\text{Hz}$), 4.67(2H, s), 4.28(2H, s)

10 **Example 7: Synthesis of 1-(3-hydroxypropyl)-2-mercapto-5-hydroxymethylimidazole**

The title compound was obtained in the yield of 69% according to the substantially same procedure as Example 1. The ^1H NMR data are as shown below.

^1H NMR (500MHz, DMSO- d_6) δ 11.96(1H, s), 6.80(1H, s), 5.19(1H, -OH), 4.56(1H, -OH), 4.35(2H, s), 4.02(2H, t, 7.3Hz), 3.40(2H, m), 1.85(2H, t, $J=7.3\text{Hz}$)

15 **<Step 2: Synthesis of a 1-substituted 5-hydroxymethylimidazole>**

Example 8: Synthesis of 1-benzyl-5-hydroxymethylimidazole

1-Benzyl-2-mercapto-5-hydroxymethylimidazole (2.2 g, 9.99 mmol) and tungstic acid (H_2WO_4 , 25 mg, 1 mol%) were mixed in 11 ml of methanol. The mixture was warmed to 40 °C in a water bath and 30% hydrogen peroxide (3.75 g, 3.2 molar eq.) was added dropwise thereto for 5 minutes while stirring. The reaction mixture was warmed to 65 °C and refluxed, and stirred at the same temperature for 2.5 hours. Upon exhaustion of the starting material, the mixture was cooled in an ice bath and thereto was added 1 N sodium hydroxide solution (18 ml) to adjust pH of the mixture to 10. The resulting solid was further stirred for 15 minutes, filtered, washed twice with 15 ml of distilled water and 15 ml of isopropyl ether, respectively, and dried to give 1.3 g (Yield 69%, HPLC purity 96.7%) of the title compound as a white powder.

30 ^1H NMR (500MHz, DMSO- d_6) δ 7.67(1H, s), 7.35(2H, t, $J=7.3\text{Hz}$), 7.28(1H, t, $J=7.3\text{Hz}$), 7.17(2H, d, $J=7.3\text{Hz}$), 6.82(1H, s), 5.23(2H, s), 5.11(1H, t, -OH), 4.32(2H, d,

J=5.5Hz)

^{13}C NMR (125MHz, DMSO- d_6) δ 163.15, 137.68, 130.91, 128.97, 127.78, 127.40, 113.39, 53.88, 46.97

5 **Example 9: Synthesis of 1-(4-bromobenzyl)-5-hydroxymethylimidazole**

1-(4-Bromobenzyl)-2-mercapto-5-hydroxymethylimidazole(1.5 g, 5 mmol) and tungstic acid(12.5 mg, 1 mol%) were suspended in 7 ml of methanol. The suspension was warmed to 40 °C and then, 30% hydrogen peroxide was slowly added dropwise. After about 2 hours, the mixture was cooled and neutralized with 1 N sodium hydroxide
10 solution, and the precipitate was filtered. The obtained solid was washed twice with 5 ml of distilled water and 5 ml of isopropyl ether, respectively, to give 1.1 g(Yield 82%) of the title compound as a white powder.

^1H NMR (500MHz, DMSO- d_6) δ 7.68(1H, s), 7.54(2H, dd, $J_1=6.4\text{Hz}$, $J_2=1.8\text{Hz}$), 7.12(2H, dd, $J_1=6.4\text{Hz}$, $J_2=1.8\text{Hz}$), 6.83(1H, s), 5.21(2H, s), 5.12(1H, s, -OH), 4.32(2H, d, $J_{\text{gem}}=3.25\text{Hz}$)
15

^{13}C NMR (125MHz, DMSO- d_6) δ 139.04, 137.66, 132.07, 129.83, 128.08, 121.22, 113.75, 53.33, 47.45

Example 10: Synthesis of 1-(3-bromobenzyl)-5-hydroxymethylimidazole

20 The title compound was obtained in the yield of 75% by employing 1-(3-bromobenzyl)-2-mercapto-5-hydroxymethylimidazole according to the substantially same procedure as Example 9.

^1H NMR (500MHz, DMSO- d_6) δ 7.71(1H, s), 7.49(1H, d, $J=7.8\text{Hz}$), 7.37(1H, s), 7.31(1H, t, $J=7.8\text{Hz}$), 7.16(1H, d, $J=7.8\text{Hz}$), 6.84(1H, s), 5.24(sH, s), 5.13(1H, s, -OH),
25 4.32(2H, d, $J_{\text{gem}}=4.6\text{Hz}$)

^{13}C NMR (125MHz, DMSO- d_6) δ 141.02, 139.11, 132.14, 131.34, 130.96, 130.31, 128.08, 126.67, 124.42, 53.28, 47.35

Example 11: Synthesis of 1-(3,4-dioxymethylenebenzyl)-5-hydroxymethylimidazole

30 1-(3,4-Dioxymethylenebenzyl)-2-mercapto-5-hydroxymethylimidazole (2.64 g, 10

mmol) and vanadium pentoxide (V_2O_5 , 18 mg, 1 mol%) were suspended in 10 ml of ethanol and 10 ml of distilled water. The suspension was warmed to about 50 °C and 30% hydrogen peroxide was slowly added dropwise thereto. After about 1 hour, the mixture was cooled and thereto was added 1 N sodium hydroxide solution to adjust the pH of the mixture to 10. The resulting mixture was filtered, washed twice with 15 ml of distilled water and 15 ml of isopropyl ether, respectively, and dried to give 2.05 g (Yield 88%) of the title compound as a white powder.

1H NMR (500MHz, DMSO- d_6) δ 7.64(1H, s), 6.87(1H, d, $J=7.5$ Hz), 6.79(2x 1H, s), 6.70(1H, d, $J=7.5$ Hz), 5.99(2H, s), 5.10(2H, s and 1H, s, -OH), 4.34(2H, s)

^{13}C NMR(125MHz, DMSO- d_6) δ 148.06, 147.23, 138.82, 132.09, 131.84, 127.93, 121.28, 108.80, 108.40, 101.62, 53.34, 47.87

Example 12: Synthesis of 1-ethyl-5-hydroxymethylimidazole

The title compound was obtained in the yield of 68% by employing 1-ethyl-2-mercapto-5-hydroxymethylimidazole according to the substantially same procedure as Example 8 except that the residue was extracted with chloroform instead of being filtered.

1H NMR (500MHz, DMSO- d_6) δ 7.59(1H, s), 6.76(1H, s), 4.43(2H, 2), 3.99(2H, q, $J=7.3$ Hz), 1.33(3H, t, $J=7.3$ Hz)

^{13}C NMR(125MHz, DMSO- d_6) δ 137.83, 131.85, 127.69, 60.92, 53.15, 16.93

Example 13: Synthesis of 1-allyl-5-hydroxymethylimidazole

The title compound was obtained in the yield of 76% by employing 1-allyl-2-mercapto-5-hydroxymethylimidazole according to the substantially same procedure as Example 8 except that the residue was extracted with n-butanol instead of being filtered.

1H NMR (500MHz, DMSO- d_6) δ 7.54(1H, s), 6.79(1H, s), 6.00(1H, ddd, $J_1=20$ Hz, $J_2=10$ Hz, $J_3=5.5$ Hz), 6.15(1H, dd, $J_1=10$ Hz, $J_2=1.35$ Hz), 4.98(1H, dd, $J_1=16.95$ Hz, $J_2=1.35$ Hz), 4.64(2H, dd, $J_1=5.5$ Hz, $J_2=1.35$ Hz), 4.39(2H, s)

^{13}C NMR(125MHz, DMSO- d_6) δ 138.47, 135.15, 132.19, 127.72, 117.37, 60.91, 47.07

Example 14: Synthesis of 1-(3-hydroxypropyl)-5-hydroxymethylimidazole

1-(3-Hydroxypropyl)-2-mercapto-5-hydroxymethylimidazole(5.0 g, 23.1 mmol) and tungstic acid(H_2WO_4 , 58 mg, 1 mol%) were mixed in 25 ml of methanol and 25 ml of distilled water. The mixture was warmed to 40 °C and 3.6 g of 30% hydrogen peroxide was added dropwise thereto. The whole mixture was stirred for 15 minutes and cooled and then, neutralized with 1 N sodium hydroxide solution. The resulting mixture was extracted twice with 25 ml of n-butanol and the solvent was distilled under reduced pressure to give 3.45 g(Yield 80.7%) of the title compound.

^1H NMR (500MHz, CDCl_3) δ 7.46(1H, s), 6.91(1H, s), 4.61(2H, s), 4.15(2H, t, J=7Hz), 3.52(2H, t, J=7Hz), 2.01(2H, m)

Example 15: Synthesis of 1-(4-bromobenzyl)-5-hydroxymethylimidazole

1-(4-Bromobenzyl)-2-mercapto-5-hydroxymethylimidazole(40 g, 0.134 mol) and vanadyl sulfate hydrate(21.9 mg, 0.1 mol%) were introduced into a mixed solution of 240 ml of ethanol and 240 ml of water. The mixture was warmed to 45 °C and stirred. After a short time, 30% hydrogen peroxide(51.6 g, 3.4 molar eq.) was slowly added dropwise thereto and the internal temperature was kept at about 50 °C. When the initial white suspension turned to a pale yellow solution, the solution was further stirred for about 30 minutes to which was added 6 N sodium hydroxide solution to adjust pH of the solution to about 10. Then, ethanol was distilled under reduced pressure. The precipitated crystal was filtered, washed with distilled water and dried to the constant weight to give 28.7 g(Yield 80.4%, HPLC=97%) of the title compound as a white powder.

^1H NMR (δ , ppm, $\text{DMSO}-d_6$) 7.68(1H, s), 7.54(2H, d, J=8.3Hz), 7.12(2H, d, J=8.3Hz), 6.82(1H, s), 5.21(2H, s), 5.09(1H, t, J=5.5Hz), 4.31(2H, s)

Example 16: Synthesis of 1-(3,4-dioxymethylenebenzyl)-5-hydroxymethylimidazole

1-(3,4-Dioxymethylenebenzyl)-2-mercapto-5-hydroxymethylimidazole(22.15 kg, 83.8 mol) and vanadyl sulfate hydrate(11 g, 0.1 mol%) were introduced into the reactor. 47.1 kg of Ethanol and 55 kg of purified water were added thereto and the temperature of the reaction solution was adjusted to 44 °C while stirring. To the above suspension was

slowly added 32.2 kg of 30% hydrogen peroxide at the temperature ranging from 40 to 60 °C. The whole mixture was stirred at 46 °C and 6 N sodium hydroxide solution was added thereto to adjust pH of the mixture to 10. Then, ethanol was distilled under reduced pressure. Upon completion of the distillation, the residue was cooled to room temperature, filtered, washed with purified water, and dried to give 11.5 kg (Yield 59.9%, HPLC=96.6%) of the title compound as a pale yellow powder.

¹H NMR (δ , ppm, DMSO-d₆) 7.64(1H, s), 6.87(1H, d, J=7.8Hz), 6.79(2H, s), 6.69(1H, d, J=7.8Hz), 5.99(2H, s), 5.10(2H, s), 4.34(2H, s)

10

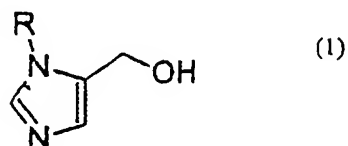
INDUSTRIAL APPLICABILITY

As described above, the 1-substituted 5-hydroxymethylimidazole of the formula (1) and the 1-substituted 2-mercapto-5-hydroxymethyl-imidazole of the formula (2) prepared according to the present process are known to be useful intermediates for preparing anticancer agents, farnesyl transferase inhibitors [J. S. Ko, et al., PCT WO99/05117 A1 19990204, p129].

According to the present process, the 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) can be more safely and rapidly prepared in higher purity and yield, as compared with the conventional preparation process. In addition, the 1-substituted 5-hydroxymethylimidazole of the formula (1) can be prepared in high yield and purity under safe reaction condition via oxidative elimination of the thiol group. Accordingly, the present process is applicable in the industrial scale preparation, since it can be safely performed without use of concentrated nitric acid.

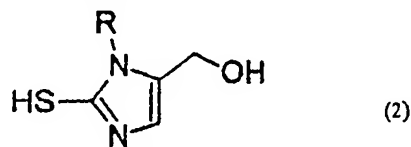
WHAT IS CLAIMED IS:

1. A process for preparing a 1-substituted 5-hydroxymethylimidazole of the formula:



- , wherein R represents alkyl, hydroxyalkyl, allyl, or substituted or unsubstituted arylmethyl or diarylmethyl,

comprising the step of reacting a 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula:



, wherein R is as defined above,

in the presence of a transition metal catalyst and an oxidizing agent in a solvent.

10

2. The process of Claim 1, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, alkyl hydrogen peroxide and alkaline hypochlorite.

3. The process of Claim 2, wherein the oxidizing agent is 10~30% hydrogen peroxide.

15

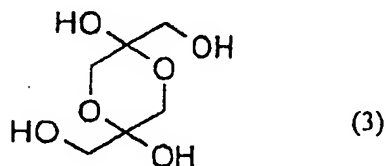
4. The process of Claim 1, wherein the transition metal catalyst is selected from the group consisting of tungstic acid(H_2WO_4), vanadium pentoxide(V_2O_5) and vanadyl sulfate($VOSO_4$).

20

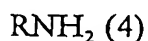
5. The process of Claim 1, wherein the molar ratio of the transition metal catalyst to the compound of the formula (2) is 0.001 ~ 0.2:1.

6. The process of Claim 1, wherein the solvent is selected from the group consisting of water, lower alcohol and a mixture thereof.

7. The process of Claim 1, wherein the 1-substituted 2-mercapto-5-hydroxymethylimidazole of the formula (2) is prepared by reacting 1,3-dihydroxyacetone dimer of the formula:



, with an acid addition salt of amine of the formula:



, wherein R is as defined in Claim 1, and

10 thiocyanate of the formula:



, wherein M represents alkali metal,

in the presence of an acid catalyst in a lower alcohol solvent.

15 8. The process of Claim 7, wherein M represents potassium.

9. The process of Claim 7, wherein the acid addition salt of amine is ammonium halide.

20 10. The process of Claim 9, wherein the ammonium halide is ammonium chloride.

11. The process of Claim 7, wherein the molar ratio of the 1,3-dihydroxyacetone dimer of the formula (3) to the acid addition salt of amine of the formula (4) is 0.5 ~ 2:1.

25 12. The process of Claim 7, wherein the molar ratio of the thiocyanate of the formula (5) to the acid addition salt of amine of the formula (4) is 1 ~ 3:1.

13. The process of Claim 7, wherein the lower alcohol is isopropanol or n-butanol.
14. The process of Claim 1 or 7, wherein R represents C₁₋₄alkyl, hydroxyC₁₋₄alkyl, allyl, benzyl, halogen-substituted benzyl or 3,4-dioxymethylenebenzyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01016

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 233/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D 233/64, A61K 31/4164

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS, NPS, PAJ, MEDLINE, CA on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

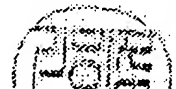
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00/01674 A1(MERCK&CO., INC.) 13 January 2000(13. 01. 00), see entire document	1-14
D, A	WO 99/05117 A1(LG CHEMICAL LTD.) 4 February 1999(04. 02. 99), abstract, claim 4	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search
14 DECEMBER 2000 (14.12.2000)Date of mailing of the international search report
15 DECEMBER 2000 (15.12.2000)Name and mailing address of the ISA/KR
Korean Industrial Property Office
Government Complex-Taejon, Dunsan-dong, So-ku, Taejon
Metropolitan City 302-701, Republic of KoreaAuthorized officer
KIM, Hee Sue

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR00/01016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 00/01674 A1	13. 01. 2000	US 6140508 A AU 4844699A1	31. 10. 2000 24. 01.
2000			
WO 99/05117 A1	04. 02. 1999	AU 8464798 A1	16. 02. 1999

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☐ FADED TEXT OR DRAWING

☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.